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Diabetic Peripheral Neuropathies (DPNs) from Basic and Clinical Aspects

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Abbreviations: DPNs-Diabetic Peripheral Neuropathies, DSPN-Distal Symmetric Polyneuropathy, DAN-Diabetic Autonomic Neuropathy, OH-Orthostatic Hypotension, NCV-Nerve Conduction Velocity, DPN-Diabetic Polyneuropathy, SNCV-Sural Nerve Conduction Velocity, SNAP-Sural Nerve Action Potential, UKPDS-UK Prospective Diabetes Study, ACCORD-Action to Control Cardiovascular Risk in Diabetes, CGM-Continuous Glucose Monitoring, T1DM and T2DM-Type 1 and 2 Diabetes Mellitus.

Diabetes has been one of the crucial diseases worldwide, which has to be controlled adequately for long years. It has three diabetic complications of micro-angiopathy such as neuropathy, retinopathy and nephropathy. Among them, Diabetic Peripheral Neuropathies (DPNs) are most prevalent to manage in primary care setting. In this article, recent topics concerning DPNs are introduced [1].

DPNs have a variety of symptoms and signs, then DPNs are often described in plural forms [2]. DPNs are classified into two categories, which are local and general. The former includes mononeuropathy and multifocal neuropathy. The latter includes diabetic polyneuropathy (DPN) and others. DPN has Distal Symmetric Polyneuropathy (DSPN) and Diabetic Autonomic Neuropathy (DAN) [2]. For examples, DSPN shows bilateral numbness of extremities and DAN shows Orthostatic Hypotension (OH).

What are DSPN and DAN like in clinical settings? We have been treating lots of diabetic patients for many years. Two conditions would be shown which are easy to understand. One is the research for DSPN, in which Sural Nerve Conduction Velocity (SNCV) and Sural Nerve Action Potential (SNAP) were measured in patients with Diabetes Mellitus (DM), Hemodialysis (HD) and control r [3]. In our study, there were four groups, which are 1) Both DM/HD, 2) DM only, 3) HD only, 4) control. The results of SNCV and SNAP showed from abnormal to normal in group 1,2,3,4, respectively, in this order [3].

Another is the situation of DAN with severe status of symptom. The case is 58 year-old man with neuropathy, retinopathy, nephropathy and remarkable OH. When he was lying position, his Blood Pressure (BP) was 164/98 mmHg. As he changed to sit on the bed, BP decreased to 140/82 mmHg. Just after standing up with 4-5 steps, his BP suddenly decreased to 98/56 mmHg associated with prompt dizziness and almost feint and unconsciousness due to OH. These phenomenon would be from typical DAN.

Author and colleagues have continued clinical practice and research for patients with Type 1 and 2 Diabetes Mellitus (T1DM, T2DM). Especially, we reported the clinical comparison of Low Carbohydrate Diet (LCD) and Calorie Restriction (CR) in T2DM. Furthermore, investigation of Latent Autoimmune Diabetes in Adults (LADA) was reported in T1DM [4-6].

In both of T1DM and T2DM, clinically important management would be Glycemic Control (GC) in the case of various situations. There was a study between the degree of GC and diabetic neuropathy [7]. It showed rather equivocal effect of DPNs for intensive GC in T2DM, which was from non-optimized HbA1c values [7]. The optimum GC values have not been shown for improving neuropathy results in T2DM by randomized trials [8].

On contrast, almost normal range of GC for more than 20 years prevented DPN in T1DM [9]. In the case of poorly controlled T2DM, Insulin-Providing Agents (IPAs) cannot bring normalization of HbA1c for long years because of potential severe hypoglycemia [8]. Consequently, the beneficial effect for normal range of HbA1c without hypoglycemia to Neuropathy Outcome Measures (NOMs) have not been studied in T2DM.

In addition to mean value of GC, Glycemic Variability (GV) [10] and metabolic various memories would influence DPN and also diabetic microangiopathies. Further, Impaired Glucose Tolerance (IGT) may exacerbate the pathophysiological changes of neuropathy as an indicator of small-fiber influence [11-13].

In the STENO-2 study, long-term rigorous glycemic control (A1c<6.5%) and multifactor intervention significantly reduced the risk of developing cardiovascular disease, nephropathy, retinopathy, and autonomic neuropathy. However, the risk of developing DSPN was not significant.

In order to prevent onset and progression of DSPN, it is important to maintain adequate GC and also GV. It is speculated from the pathology of IGT neuropathy [14,15].

There is a recently significant report that both neuropathy of small-diameter and large-diameter were significant related to strict GC around average HbA1c 6.1%. It could avoid not only hypoglycemia, but also GV, which were associated with stable management of body weight, blood pressure and lipid [16]. In the case of T2DM with relatively short duration, DPN could be improved by total care of GC and GV [16].

Regarding the evaluation of neuropathy, there has been a standard classification for the severity of neuropathy, which is the Toronto Consensus on Diabetic Neuropathies [17]. It considers a confirmed DPN as a combination of the presence of abnormal Nerve Conduction Velocity (NCV) and a symptom, or a sign. As a result, patients with NDS>2 and Sensory NCV of Sural Nerve (SNCV) <42 m/s were usually estimated as the presence of the neuropathy. This criteria have been applied for lots of reports about neuropathy [3].

In T2DM, intensive GC has been said to reduce diabetic micro vascular complications. Then, continuation of strict GC may prevent and ameliorate DPN. The intensive GC in T2DM is associated with a reduction in micro vascular complications. The strict GC may prevent and/or ameliorate the progress of DPN. However, Kumamoto Study showed that strict GC level as HbA1c 7.1% prevented NCV in T2DM [18]. In the UK Prospective Diabetes Study (UKPDS), the intensive and conventional GC as HbA1c 7.0% vs. 7.9% showed a similar effect on DPN [19]. Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial showed that intensive care as HbA1c 6.3% prevented loss of ankle reflex and light-touch sensation but increased CVD-related mortality and severe hypoglycemia [8]. Consequently, these studies could not establish the optimum GC value for preventing the neuropathy deterioration in T2DM.

In order to obtain the beneficial effect in the light of diabetic complication, it would be necessary to maintain tight GC more than 3-5 years. In T2DM, chronic hyperglycemia has played a crucial role in progress of DPN. Furthermore, metabolic syndrome components would probably cause pathophysiological neuropathy. Glucose intolerance and obesity may have a role in progress of neuropathy. However, hyperlipidemia and hypertension showed equivocal results for neuropathy. In addition to GC, GV has been crucial factor to glucose variability. GV may show risk for progress of DPN apart from HbA1c values. From the cross-sectional investigation of T2M, GV showed a relationship with DPN value, which was studied by Continuous Glucose Monitoring (CGM). In these studies, GV data from CGM had been evaluated in the cross-sectional study associated with DPN data [20-25].

There is a recent significant report [26]. It was the neurophysiological comparison between two groups of subnormal level of HbA1c 6.5% and conventional treatment of HbA1c 7.2%. The former group showed formerly uncontrolled situation, but maintaining the HbA1c level for 4 years could bring the improvement of neurophysiological and some corneal nerve fiber measures. In contrast, the latter group showed the deteriorated data at the level of 7.2% [26]. Consequently, the standard level of diabetes care as HbA1c 7.0% does not seem to be enough for DPN.

Regarding diabetic neuropathy, recent research shows the several related genes, such as Aldose Reductase Gene (AKR1B1), Vascular Endothelial Growth Factor (VEGF), 5,10-Methylene-Tetrahydrofolilate Reductase (MTFR), Apolipoprotein E (APOE) and Angiotensin Converting Enzyme (ACE) genes. They would contribute significantly in the pathogenesis of DN, and may serve as biomarkers to predict future progress of neuropathy development and/or treatment response [27].

In summary, recent topics concerning diabetic neuropathy were described. Diabetic practice and various researches have been in progress for long, and this article would be expected to become useful reference for future development in diabetes.

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